REPLY PURSUANT TO 37 C.F.R. § 1.111

REMARKS

Claims 1-9 are currently pending in the application. Claims 1-9 are rejected. By way of this amendment claims 1-9 are cancelled and new claims 10-19 (corresponding to claims 2-9) are added. Cancelled claim 1 was not replaced.

In addition, substitution of specified sections or paragraphs of the specification is requested to amend typographical and other simple inadvertent errors noted therein by applicants. All amendments to the specification and the claims have been made in accordance with the procedures set out in 37 C.F.R. § 1.121, and a marked-up version of the amendments is appended hereto in accordance with 37 C.F.R. § 1.121. No new subject matter has been added through these amendments.

AMENDMENTS TO THE SPECIFICATION OTHER THAN THE CLAIMS UNDER 37 C.F.R. § 1.121 (b)

The following is a summary describing the specific amendments to each section of the specification other than the claims under 37 C.F.R. § 1.121 (b), wherein it is requested to replace specific sections of the specification to correct typographical and other inadvertent errors noted by applicants.

For replacement of the section on page 5, starting at line 5 and ending at line 11:

At line 10, delete "iso-ismotic" and insert in its place --iso-osmotic--

This amendment corrects the inadvertent typographical error wherein the word "iso-ismotic" should properly read "iso-osmotic".

For replacement of the section on page 7, starting at line 17 and ending at line 26:

At line 17, delete "(-)-cis-2-(2-Chlorophenyl)-5,7-dimethoxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one" and insert in its place --(-)-cis-2-(2-

chlorophenyl)-5,7-dimethoxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one--

This amendment replaces the inadvertently typed upper case "C" in 2-Chlorophenyl with a lower case "c".

At lines 21 to 23, delete "The resulting mixture is basified to pH 7.5-8.5 using saturated sodium carbonate solution. A mixture of ethanol twice with a mixture of ethanol and chloroform." and insert in its place --The resulting mixture is basified to pH 7.5-8.5 using saturated sodium carbonate solution, and extracted twice with a mixture of ethanol and chloroform.--

This amendment corrects an inadvertent simple drafting error with respect to the description of the extraction procedure.

At lines 24 to 25, delete "(+)-cis-2-(2-chloropheny)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one" and insert in its place --(+)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one--

This amendment corrects the inadvertent omission of the second occurrence of the letter "l" from "2-chlorophenyl".

For replacement of the section on page 7, starting at line 28 and ending on page 8 at line 2:

Page 7, at lines 24 to 25, delete "(+)-cis-2-(2-chloropheny)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one" and insert in its place --(+)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one--

This amendment corrects the inadvertent omission of the second occurrence of the letter "l" from "2-chlorophenyl".

Page 7, line 30, delete "minute" and in its place insert --minutes--

This amendment corrects the inadvertent omission of the "s" from "minutes".

Page 7, at lines 24 to 25, delete "(+)-cis-2-(2-chloropheny)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one" and insert in its place --(+)-

cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one--

This amendment corrects the inadvertent omission of the second occurrence of the letter "l" from "2-chlorophenyl".

For replacement of the section on page 8, starting at line 4 and ending at line 10:

At lines 9 to 10, delete "(-)-cis-2-(2-chloropheyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4-H-1-benzopyran-4-one" and insert in its place --(-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4-H-1-benzopyran-4-one--

This amendment corrects the inadvertent omission of the letter "n" in "2-chlorophenyl" on line 9 and the extraneous dash from "4-H" to read "4H" on line 10 in the compound name.

For replacement of the section on page 8, starting at line 12 and ending at line 20:

At lines 12 to 13, delete "(-)-cis-2-(2-chloropheyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4-H-1-benzopyran-4-one" and insert in its place --(-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4-H-1-benzopyran-4-one--

This amendment corrects the inadvertent omission of the letter "n" in "2-chlorophenyl" on line 9 and the extraneous dash from "4-H" to read "4H" on line 10 in the compound name.

At line 15, after the word "filter" insert --cake--

This amendment corrects the inadvertent omission of the word "cake" from the sentence "The filter cake is rinsed with hot ethanol."

At lines 19 to 20, delete "(-)-cis-2-(2-chloropheyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4-H-1-benzopyran-4-one" and insert in its place --(-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4-H-1-benzopyran-4-one--

This amendment corrects the inadvertent omission of the letter "n" in "2-chlorophenyl" on line 9 and the extraneous dash from "4-H" to read "4H" on line 10 in the compound name.

For replacement of the section on page 12 titled "Abstract of the Invention"

On page 12, line 4, before "(FormII)", insert --hydrochloride--

This amendment corrects the inadvertent omission of "hydrochloride" for from the compound name.

AMENDMENTS TO THE CLAIMS UNDER 37 C.F.R. § 1.121 (c)

Claims 1-9 are cancelled and new claims 10-19 are added. The following table lists the correspondence of original claims 1-9 to new claims 10-19.

Original Claim Number	New Claim Number
1	-----
2	10
3	11
4	12
5	13
6	14
7	15
8	16
9	17-19

REJECTIONS

Section 2 of the Office Action - Rejection under 35 USC 112, second paragraph:

Original claims 1, 8 (new claim 16), and 9 (new claims 17-19) stand rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically the examiner has noted that the instant claims are drawn to Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one while the specification defines Form II as (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-

8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate. Claims 1-9 were cancelled and are replaced by new claims 10-19.
Cancelled original claim 1 was not replaced by any of the new claims. Original claim 8 was replaced by new claim 16 and original claim 9 was replaced by new claims 17, 18 and 19 that are each drawn to Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate as defined in the specification (page 1, lines 32-33 to page 2, lines 1-2), versus the original claims that were drawn to Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one. Thus, the examiner's allegation that original claims 1, 8 and 9 are ambiguous with respect to the definition of Form II in the specification has been rectified.

Applicants respectfully request withdrawal of this rejection.

Section 3 of the Office Action - Rejection under 35 USC § 103(a)

Claims 1-4, 8-9 are rejected under 35 USC 103(a) as being unpatentable over Kattige et al. US 4,900,727 and Sedlacek et al. (Int. J. Oncology, vol. 9, pgs 1143-1168) in the event that the claims are drawn to a new form of an old product cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one.

The examiner alleges that Kattige '727 dislcoses a solid form of cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one [claim 4 is directed to the racemate of the compound and its pharmaceutically acceptable salts] and Sedlacek et al. disclose (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride dihydrate (page 1146) and its pharmacological efficacy in treating cancer, inhibiting protein kinase or cyclin dependent kinase (p1146-1164).

The examiner further alleges the Kattige '727 and Sedlacek et al. disclosed all of the elements of the claims except the physical nature of the solid material was not described. Furthermore the examiner finds the instant claims being drawn to the particular crystalline form II (reads form I in the office action) prima facie obvious over the art because changing the form, purity or other characteristic of an old product does not render the novel

form patentable when the change is a mere difference in degree of purity or physical character of the "product" for which the chemical nature and therapeutic activity were the same (In re Cofer 148 USPQ 268, Ex parte Schmidt-Kastner 153 USPQ 473).

Claims 1-9 were cancelled and replaced by claims 10-19. New claims 10-12 correspond to original claims 2-4, new claim 16 corresponds to original claim 8 and new claims 17-19 correspond to original claim 9.

Applicants respectfully traverse this rejection. Kattige '727 discloses solid forms of cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one as the racemic hydrochloride monohydrate, the dextrorotatory hydrochloride dihydrate and the levorotatory hydrochloride sesquihydrate (see Tables 5 and 9). Sedlacek et al. dislcose (-)cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride dihydrate as a solid form. The prior art and the claimed subject matter differ in that the claimed subject matter is an ethanol solvate of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride obtained in a crystalline form that displays a characteristic X-ray diffraction pattern. There is no motivation or suggestion in Kattige '727 or in Sedlacek et al. that would prompt one of ordinary skill in the art to prepare an alcohol solvate of (-)cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride. Indeed "before the PTO may combine the disclosures of two or more prior art references in order to establish *prima facie* obviousness, there must be some suggestion or incentive for doing so.." (see *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ.2d 1596, 1598-99 (Fed. Cir. 1988).

Furthermore, an evaluation of obviousness of the invention as a whole requires looking not only to the subject matter which is literally recited in the claim in question but also to the properties of the subject matter which are inherent in the subject matter and are disclosed in the specification (*In re Antonie* 559F.2d 618, 619, 195 USPQ 6, 8 (CCPA 1977). The claimed invention is an ethanol solvate of (-)cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride that is a distinct composition as evidenced by its physical characteristics that are supported by X-ray diffraction pattern data in the specification. Additionally, the ethanol solvate has the inherent advantage of less toxicity as disclosed in the specification

with respect to the methanol solvate. Thus, there is more at hand herein than merely changing the degree of purity or physical character of the product, and the invention as a whole should have been evaluated versus the analysis of the invention provided by the examiner based solely on prior art hydrate forms of (-)cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride.

Thus, in light of the above, applicants respectfully request withdrawal of the rejection to the affected claims.

Section 4 of the Office Action - Rejection under 35 USC § 103(a)

Claims 1-9 are rejected under 35 USC 103(a) as being unpatentable over Kim US 5,908,934 ('934) in view of Cheronis ["Semimicro Experimental Organic Chemistry", DeGratt, p. 32-35 (1958)] and Evans ["An Introduction to Crystal Chemistry", Cambridge Press, p. 393-397 (1964)] in the event the claims are drawn to an ethanol solvate of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride. The examiner alleges that Kim '934 disclosed the methanol solvate of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride and analogous process in preparing the solvate (col. 9 lines 50-57). The examiner further alleges that Kim '934 disclosed all the elements of the claims except the solvent employed by Kim '934 is methanol and during the crystallization stage a paired solvent of methanol/ether was used, while instant claims are drawn to the homologous ethanol. Cheronis teaches that the choice of solvent in crystallization is empirical and one should experimentally select under the general guidelines (see p 32, section 5.3), and that when the solubility of the compound in a particular solvent is too high, solvent pair may be employed (see p 35). The examiner alleges that one having ordinary skill in the art would find the claimed product and process prima facie obvious over Kim because:

(i) a person having ordinary skill in the art is deemed to be aware that (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride methanol solvate is an organic clathrate, that the guest molecules are mechanically imprisoned in the framework of the host and that the next higher homolog of methanol, i.e. ethanol, would be a close analog for such clathrate formation.

(ii) a person having ordinary skill in synthetic chemistry in possession of the exemplified process and product of methanol solvent by Kim '934 and the laboratory manual of Cheronis would be motivated to empirically modify the process with the next homologous alcohol with the expectation that the ethanol solvate with a different solubility can be obtained without pairing solvents.

Original claims 1-9 are cancelled. Original claims 2-8 were replaced by new claims 11-16, respectively, and original claim 9 was replaced by new claims 17-19.

Applicants respectfully traverse this rejection. The examiner's interpretation that the Kim '934 patent, column 9, example D, discloses the methanol solvate of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride and analogous process in preparing the solvate (col. 9 lines 50-57) is not convincing. The critical sentence in Kim '934, column 9, starting on line 53 reads:

"The precipitated solid was filtered, washed with ethyl ether three times and dried to afford a solid, 6.7 g which contained the title compound methanol."

As written the sentence is ambiguous with respect to the meaning or context of the word "methanol". To one of ordinary skill in the art, the nature of the material so obtained is unclear, and no evidence supporting the true nature of the material obtained at this point in the procedure was provided. Indeed the word "methanol" could be viewed as just an extraneous word due to a simple drafting error and that "methanol" was not actually intended to be included in the above-quoted sentence. The only thing clearly stated by the quoted sentence is that the title compound was obtained. It would appear that the examiner presumed the material to be a methanol solvate for the purpose of formulating the rejection. Obviousness under 35 USC 103 is a legal conclusion based on factual evidence (Stratoflex, Inc. v Aeroquip Corp., 713 F.2d 1530, F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). The examiners analysis is not based on clear factual evidence since the identity of the material obtained by Kim '934 is not ascertainable with any degree of certainty by one of ordinary skill in the art. Thus, the examiner's analysis required by MPEP 706.02(j) to establish a prima facia case of obviousness is flawed, Kim '934 did not disclose all the elements of the claims as maintained by the examiner and the use of Kim '934 as a reference would appear improper.

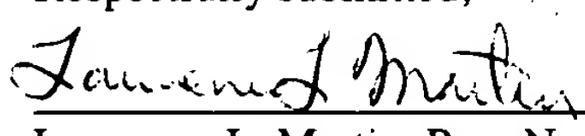
Applicants respectfully request withdrawal of the rejection to the affected claims.

CONCLUSION

Applicants respectfully submit that the claims 10-19 are now in condition for allowance and respectfully requests a notice to this effect. Should the Examiner have any questions please call (collect if necessary) the undersigned agent at the telephone number listed below.

Applicants concurrently submit herewith a petition for a 3-month extension of time to make this response timely. The Commissioner is hereby authorized to charge these fees and any other fees that are due to this paper to Deposit Account No. **18-1982** for Aventis Pharmaceuticals Inc., Bridgewater, NJ. Please credit any overpayment to Deposit Account No. **18-1982**.

Respectfully submitted,



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Aventis Docket No. HMR2041 US NP1

VERSION WITH MARKINGS TO SHOW CHANGES MADE IN THE SPECIFICATION

The marked-up version of amended secti ns of the specificati n that follow uses the following notations:
Additions are underlined, e.g., <u>XXXX</u>. In addition, text was bolded to further accent additions.
Deletions are stricken, e.g., ~~XXXX~~. A vertical line appears in the right margin to also indicate that a deletion was made.

For the section on page 5, starting at line 5 and ending at line 11:

A "pharmaceutically acceptable carrier" is an agent which is non-toxic, does not interfere with the therapeutic profile of Form II and is appropriate to the method of administration. Form II is preferably administered by the intravenous route over an appropriate period of time for cancer chemotherapy. Preferably, Form II is mixed with one or more pharmaceutically acceptable carriers. For example, Form II may be mixed with ~~iso-ismotic~~ <u>iso-osmotic</u> and pH controlled liquids such as water, dextrose/water or saline/water for injection intravenously into the patient.

For the section on page 7, starting at line 17 and ending at line 26:

To ~~(-) cis-2-(2-Chlorophenyl)-5,7-dimethoxy-8-[4R-(3S-hydroxy-1-methyl)-piperidinyl]-4H-1-benzopyran-4-one~~ <u>(-)-cis-2-(2-chlorophenyl)-5,7-dimethoxy-8-[4R-(3S-hydroxy-1-methyl)-piperidinyl]-4H-1-benzopyran-4-one</u>, quinoline and pyridine hydrochloride are added. The resulting mixture is heated to 160-190°C while stirring. Stirring is continued while maintaining the temperature at 160-190°C for 2 hours. After cooling the reaction mixture to 90-110°C water is added. ~~The resulting mixture is basified to pH 7.5-8.5 using saturated sodium carbonate solution. A mixture of ethanol twice with a mixture of ethanol and chloroform.~~ <u>The resulting mixture is basified to pH 7.5-8.5 using saturated sodium carbonate solution, and extracted twice with a mixture of ethanol and chloroform.</u> The combined extracts are evaporated to dryness to obtain ~~(+) cis-2-(2-chloropheny)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one~~ <u>(+)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one</u> crude as a brown gum, which is purified as follows.

For the section on page 7, starting at line 28 and ending on page 8 at line 2:

To ~~(+) cis 2 (2 chloropheny) 5,7 dihydroxy 8 [4R (3S hydroxy 1 methyl)piperidinyl] 4H 1 benzopyran 4 one~~ (+)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran--4-one crude, acetone is added. The resulting mixture is stirred at 55-60°C for 30-60 ~~minute~~ minutes, then cooled to 15-20°C and stirred for another 1-2 hours. The precipitated solid is isolated by filtration, washed twice with acetone and dried under reduced pressure to give ~~(+) cis 2 (2 chloropheny) 5,7 dihydroxy 8 [4R (3S hydroxy 1 methyl)piperidinyl] 4H 1 benzopyran 4 one~~ (+)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one in a purified form.

For the section on page 8, starting at line 4 and ending at line 10:

The free base from the previous step is suspended in ethanol and acidified using concentrated hydrochloric acid at such a rate that the temperature does not exceed 30°C. During this process initially all of the solid dissolves and then the hydrochloride precipitates. The suspension is cooled to 0-10°C and stirred for 1 hour while maintaining the temperature. The crystals are isolated by filtration and washed with cold ethanol to yield ~~(-) cis 2 (2 chloropheyl) 5,7 dihydroxy 8 [4R (3S hydroxy 1 methyl)piperidinyl] 4 H 1 benzopyran 4 one~~ (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4-H-1-benzopyran-4-one hydrochloride, crude.

For the section on page 8, starting at line 12 and ending at line 20:

To ~~(-) cis 2 (2 chloropheyl) 5,7 dihydroxy 8 [4R (3S hydroxy 1 methyl)piperidinyl] 4 H 1 benzopyran 4 one~~ (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride, crude, ethanol is added. The resulting mixture is heated to 70-79°C, stirred for 1 hour while maintaining the temperature and then filtered while still hot. The filter cake is rinsed with hot ethanol. The filtrate is concentrated by atmospheric distillation, until about 50% to about 90% of the volatiles have been removed. The remaining suspension is then cooled to 0-10°C while isolated by filtration and dried under reduced pressure to give the ethanol solvate of ~~(-) cis 2 (2 chloropheyl) 5,7 dihydroxy 8 [4R (3S hydroxy 1 methyl)piperidinyl] 4 H 1 benzopyran 4 one~~ (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride, purified as a yellow solid.

For the section on page 12 titled "Abstract of the Invention"

Abstract of the Invention

An ethanol solvate form of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride (Form II), a method of making Form II and a composition comprising Form II.